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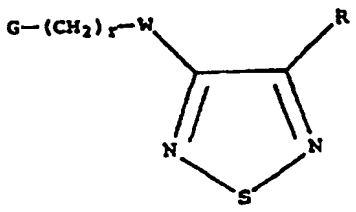
(54) Title: A METHOD OF TREATING HYPERCHOLESTEROLEMIA AND RELATED DISORDERS

(57) Abstract

The present invention relates to novel method for treating a mammal suffering from hypercholesterolemia and related disorders comprising administering to said subject an effective amount of a compound of formula (I).



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A Method of Treating Hypercholesterolemia and related Disorders

Field of the Invention

The present invention relates to the use of a class of compounds which are squalene synthetase inhibitors in the treatment of diseases associated with undesirable cholesterol levels in the body, and particularly diseases of the cardiovascular system, such as atherosclerosis.

Background of the Invention

Hypercholesterolemia is known to be one of the prime risk factors for ischemic cardiovascular disease, such as arteriosclerosis. An important risk factor for the development of atherosclerosis is an atherogenic lipid profile i.e. hyperlipidaemia with increased LDL-cholesterol and relatively decreased HDL-cholesterol.

Typically, cholesterol is carried in the blood of warm blooded animals in certain lipid-protein complexes such as chylomicrons, very low density lipoprotein (VLDL), low density lipoprotein (LDL) and high density lipoprotein (HDL). It is widely accepted that LDL functions in a way that directly results in deposition of the LDL cholesterol in the blood vessel wall and that HDL functions in a way that results in the HDL picking up the cholesterol from the vessel wall and transporting it to the liver where it is metabolized (Brown and Goldstone, Ann. Rev. Became. 52, 223 (1983); Miller, Ann. Rev. Med. 31, 97 (1980)). It is generally accepted by those skilled in the art that reduction of abnormally high LDL (low density lipoprotein) cholesterol levels is effective therapy not only in the treatment of hyper-cholesterolemia but also in the treatment of atherosclerosis.

The enzyme squalene synthase (also known as squalene synthetase) is the enzyme involved in the first committed step in the de novo cholesterol biosynthesis.

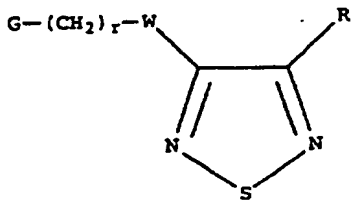
This enzyme is a microsomal enzyme that catalyses the reductive dimerization of two molecules of farnesyl diphosphate to form squalene. Squalene is utilized only for cholesterol biosynthesis whereas farnesyl diphosphate serves as the precursor to several other biologically important compounds. The inhibition of squalene synthase would thus hinder cholesterol biosynthesis while leaving unhindered other essential pathways to e.g dolichol, ubiquinone, isopentyl tRNA and prenylated proteins.

Even though there has already been discovered squalene synthetase inhibitors a need still remains for a more effective squalene synthetase inhibitor i.e. one that provides a better antihypercholesteremic effect and exhibits a good safety profile.

We have discovered a new class of squalene synthetase inhibitors which have not previously been considered for the use in treating hypercholesterolemia and related disorders.

Summary of the Invention

The method of this invention comprises administering to a patient suffering from hypercholesterolemia and related disorders an effective amount of a compound of formula I



(I)

wherein

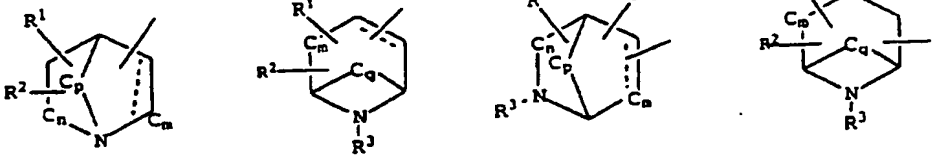
W is oxygen or sulphur; and

R is R^4, $-OR^4$, $-SR^4$, $-SOR^4$, $-SO_2R^4$, C_{3-10}-cycloalkyl, C_{4-12}-(cycloalkylalkyl), $-Z-C_{3-10}$-cycloalkyl or $-Z-C_{4-12}$-(cycloalkylalkyl), wherein Z is oxygen or sulphur, R^4 is C_{1-15}-alkyl, C_{2-15}-alkenyl or C_{2-15}-alkynyl, each of which is optionally substituted with one or more halogen(s), $-CF_3$, -CN, Y, phenyl or phenoxy, wherein phenyl or phenoxy is optionally substituted with halogen, -CN, C_{1-4}-alkyl, C_{1-4}-alkoxy, $-OCF_3$, $-CF_3$, $-CONH_2$ or $-CSNH_2$, and Y is as defined below; or

R is phenyl or benzyloxycarbonyl, each of which is optionally substituted with halogen, -CN, C_{1-4}-alkyl, C_{1-4}-alkoxy, $-OCF_3$, $-CF_3$, $-CONH_2$ or $-CSNH_2$; or

R is -Z-Y, $-O-R^5-Z-Y$, $-S-R^5-Z-Y$, $-O-R^5-Z-R^4$ or $-S-R^5-Z-R^4$ wherein Z is oxygen or sulphur, R^5 is C_{1-15}-alkylene, C_{2-15}-alkenylene or C_{2-15}-alkynylene, R^4 is as defined above, and Y is a 5 or 6 membered heterocyclic group containing one to four N, O or S atom(s) or a combination thereof, which heterocyclic group is optionally substituted at carbon and/or nitrogen atom(s) with C_{1-6}-alkyl, $-CF_3$, phenyl, benzyl or thienyl, or a carbon atom in the heterocyclic group together with an oxygen atom form a carbonyl group, or which heterocyclic group is optionally fused with a phenyl group; and

G is selected from one of the following azabicyclic ring systems



wherein R^1 and R^2 may be present at any position, including the point of attachment of the $(CH_2)_r$-W group, and independently are hydrogen, C_{1-5}-alkyl, C_{2-5}-alkenyl, C_{2-5}-alkynyl, C_{1-10}-alkoxy, C_{1-5}-alkyl substituted with -OH, halogen, $-NH_2$, carboxy or phenyl; and

R^3 is hydrogen, C_{1-5}-alkyl, C_{2-5}-alkenyl or C_{2-5}-alkynyl; and

n is 0, 1 or 2; and

m is 0, 1 or 2; and

p is 0, 1 or 2; and

q is 1 or 2; and

r is 0,1 or 2; and

..... is a single or double bond; or a pharmaceutically acceptable salt thereof.

Examples of such salts include inorganic and organic acid addition salts such as hydrochloride, hydrobromide, sulphate, phosphate, acetate, fumarate, maleate, citrate, lactate, tartrate, oxalate, or similar pharmaceutically acceptable inorganic or organic acid addition salts, and include the pharmaceutically acceptable salts listed in Journal of Pharmaceutical Science, 66, 2 (1977) which are hereby incorporated by reference.

Especially preferred salts include tartrate and hydrochloride.

The terms alkyl, alkenyl, alkynyl, alkoxy, alkylene, alkenylene and alkynylene are intended to mean straight or branched alkyl, alkenyl, alkynyl, alkoxy, alkylene, alkenylene and alkynylene.

Typical C_{1-6}-alkyl(ene) groups include, but are not limited to, methyl(ene), ethyl(ene), n-propyl(ene), iso-propyl(ene), butyl(ene), iso-butyl(ene), sec.-butyl(ene), tert.-butyl(ene), pentyl(ene), hexyl(ene) and the like.

Typical "C_{2-15}-alkenyl(ene)" groups include but are not limited to 1-propenyl(ene), 2-propenyl(ene), 1,3-butadienyl(ene), 1-butenyl(ene), hexenyl(ene), pentenyl(ene) and the like.

Typical "C_{2-15}-alkynyl(ene)" groups as used herein include, but are not limited to, 1-propynyl(ene), 2-propynyl(ene), 2-butynyl(ene), 1-pentynyl(ene), 2-pentynyl(ene) and the like.

Typical "C_{1-10}-alkoxy" groups include but are not limited to methoxy, ethoxy, propoxy and butoxy.

Typical 5 or 6 membered heterocyclic groups containing one to four N, O or S atom(s) or a combination thereof include but are not limited to pyrrole, imidazole, pyrazole, triazole, pyridine, pyrazine, pyrimidine, pyridazine, isothiazole, isoxazole, oxazole, oxadiazole, thiadiazole, quinoline, isoquinoline, quinazoline, quinoxaline, indole, benzimidazole, benzofuran, pteridine and purine.

As used herein, the term "halogen" means F, Cl, Br and I. Especially preferred halogens include Cl, Br and I.

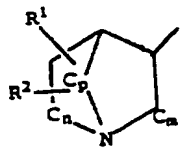
It is to be understood that the invention extends to each of the stereoisomeric forms of the compounds of formula I as well as the racemates.

As used herein, the term patient includes any mammal which could benefit from treatment of hypercholesterolemia and related disorders. The term particularly refers to a human patient, but is not intended to be so limited.

The thiadiazole compounds used in the present claimed method have been disclosed and claimed in EP 0709381A1 herein incorporated by reference in its entirety. The thiadiazole compounds are known to be useful in the treatment of ilnesses whose clinical manifestations are due to cholinergic deficiency.
Such ilnesses include Alzheimer's disease, Huntingtons chorea, tardive dyskinesia, hyperkinesia, mania and Tourette Syndrome. Accordingly there is no disclosure in this reference of using the compounds to treat hypercholesterolemia and related disorders.

The invention also comprises the use of a compound of formula I or a pharmaceutically acceptable salt thereof for the preparation of a medicament for inhibiting squalene synthetase, especially a medicament for the treatment of hypercholesterolemia.

Preferred compounds for use in treating hypercholesterolemia and related disorders are compounds wherein G is the ring system:



and wherein m and n are 1, and p is 2.

More preferred compounds include:

(±)-3-Methoxy-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-Ethoxy-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-Propyloxy-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-Butyloxy-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-Pentyloxy-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-Hexyloxy-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-(4-Methylpentyloxy)-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-Propylthio-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-Butylthio-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-Pentylthio-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(S)-3-Pentylthio-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-Hexylthio-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-(3,3-Dimethylbutylthio)-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-(2-(2-Thienylthio)ethylthio)-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-(2,2,3,3,3-Pentafluoropropylthio)-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-(3-(2-Thienyl)propylthio)-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-Butylthio-4-((1-azabicyclo[2.2.2]octan-3-yl)methoxy)-1,2,5-thiadiazole,

(±)-Exo-3-pentylthio-4-(1-azabicyclo[3.2.1]octyl-6-oxy)-1,2,5-thiadiazole,

(±)-Endo-3-pentylthio-4-(1-azabicyclo[3.2.1]octyl-6-oxy)-1,2,5-thiadiazole,

(±)-Endo-3-butyloxy-4-(1-azabicyclo[2.2.1]heptyl-3-oxy)-1,2,5-thiadiazole,

(±)-Exo-3-butyloxy-4-(1-azabicyclo[2.2.1]heptyl-3-oxy)-1,2,5-thiadiazole,

(R)-3-Pentylthio-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-(4-Methylpentylthio)-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-(3-Phenylpropylthio)-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-(4-Cyanobenzylthio)-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-(4-Fluorobenzylthio)-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-(2-Phenylethylthio)-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-(2-Phenyloxyethylthio)-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

Endo-3-butyloxy-4-(N-methyl-8-azabicyclo[3.2.1]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-Exo-3-butyloxy-4-(6-(N-methyl-8-azabicyclo[3.2.1]octan-3-onoxy))-1,2,5-thiadiazole,

(±)-Endo-3-(4-cyanobenzylthio)-4-(1-azabicyclo[3.2.1]octyl-6-oxy)-1,2,5-thiadiazole,

(±)-3-(2-(2-Thio-5-trifluoromethylthienyl)ethylthio)-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-(2-(5-(2-Thienyl)thienyl)thio)-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-(2-(2-(5-(2-Thienyl)thienyl)thio)ethylthio)-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-(2-Thienylthio)-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-(3-N-(2-Thiazolidonyl)propylthio)-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

3-Butylthio-4-(exo-2-azabicyclo[2.2.2]oct-6-yloxy)-1,2,5-thiadiazole,

Endo-3-(3-Butylthio-1,2,5-thiadiazol-4-yloxy)-1-azabicyclo[2.2.1]heptane,

Endo-3-(3-propylthio-1,2,5-thiadiazol-4-yloxy)-1-azabicyclo[2.2.1]heptane,

Endo-3-(3-Propylsulfonyl-1,2,5-thiadiazol-4-yloxy)-1-azabicyclo[2.2.1]heptane,

Endo-3-(3-(3-(4-Fluorophenyl)-2-propynyl-1-oxy)-1,2,5-thiadiazol-4-yloxy)-1-azabicyclo[2.2.1]heptane,

Endo-3-(3-(3-phenyl-2-propynyl-1-oxy)-1,2,5-thiadiazol-4-yloxy)-1-azabicyclo[2.2.1]-heptane,

Endo-3-(3-Trifluoropropylthio-1,2,5-thiadiazol-4-yloxy)-1-azabicyclo[2.2.1]heptane,

Endo-3-(3-Trifluorobutylthio-1,2,5-thiadiazol-4-yloxy)-1-azabicyclo[2.2.1]heptane,

Endo-3-(3-(4-Cyanobenzylthio)-1,2,5-thiadiazol-4-yloxy)-1-azabicyclo[2.2.1]heptane,

Exo-3-(3-Propylthio-1,2,5-thiadiazol-4-yloxy)-1-azabicyclo[3.3.1]nonane,

Exo-3-(3-Butylthio-1,2,5-thiadiazol-4-yloxy)-1-azabicyclo[3.3.1]nonane,

or a pharmaceutically acceptable salt thereof.

Methods

a) Rat liver microsomal preparation

Male rats weighing 200 to 300 g were decapitated and the liver removed and placed in 10 ml icecold 0.25 M sucrose, 2mM EDTA and 50 mM Tris, HCl buffer pH 7.4. The liver was homogenized in 3 x volume buffer relative to weight using a glass teflon Potter-Elvehjem homogenizer set to 1000 rpm. The homogenate was then centrifuged for 15 min. at 12,000 x g at 4°C. The resultant supernatant was gently decanted into 10

ml ultracentrifuge vials and treated at 100,000 x g for 60 min. at 4°C. The microsomal pellet was resuspended in a final volume of 1 ml icecold 0.1 M phosphate buffer pH 7.4 per gram liver tissue by gentle homogenization in a glass Potter-Elvehjem at 800 rpm. Aliquots of 0.5 ml (ca. 20 mg/ml protein) was stored at -80°C until further use in the squalene synthetase inhibition assay.

b) Assay procedure

To begin assay, 20 ml of the compound of this invention or vehicle solution is added to each 16 x 150 screw-cap culture tube on ice. Then 580 ml of N_2 flushed assay buffer is pipetted into each tube. 100 ml of cofactor is next added to each tube, followed by 100 ml of a dilution of microsomal enzyme (approximately 80 mg protein). The tubes are preincubated for 10 min. at 37°C, and 200 ml of the ^{3}H-FPP (200,000 dpm, 10 mM final conc.) is added to each tube at weo second intervals.

The tubes are then incubated for exactly 10 min., shaking at 150 oscillations per min. After the 10 min. incubation, the reaction is stopped by the addition of 1 ml of 15% KOH in ethanol, and the tubes are incubated for 30 min. in a 65°C water bath for saponification of lipids and solubilization of proteins. The tubes are cooled on ice for five min. The samples are next extracted with 5 ml of petroleum ether by shaking for 10 min. at low speed on a metabolic shaker. Each lower aqueous layer is frozen in a dry ice/alcohol bath (2-propanol/methanol, 1:1), and each organic layer is poured into another set of 16 x 150 screw-top culture tubes containing 2 ml of deionized water. Each ether layer is washed by vortexing each tube for 5 sec. The aqueous layers are again frozen in the dry ice/alcohol bath, and the ether is poured into scintillation vials. 10 ml of AquaSol® is next added to each vial, and the vials are counted for 5 min. in a scintillation counter. Percent inhibitions are calculated from the counts obtained.

The compounds used in this method are effective over a wide dosage range. For example, in the treatment of adult humans, dosages from about 0.05 to about 100 mg, preferably from about 0.1 to about 100 mg, per day may be used. A most preferable dosage is about 10 mg to about 70 mg per day. In choosing a regimen for patients suffering from hypercholesterolemia and related disorders it may frequently be neces-

sary to begin with a dosage of from about 30 to about 70 mg per day and when the condition is under control to reduce the dosage as low as from about 1 to about 10 mg per day. The exact dosage will depend upon the mode of administration, form in which administered, the subject to be treated and the body weight of the subject to be treated, and the preference and experience of the physician or veterinarian in charge.

The route of administration may be any route, which effectively transports the active compound to the appropriate or desired site of action, such as oral or parenteral e.g. rectal, transdermal, subcutaneous, intravenous, intramuscular, topical, intranasal or an ointment, the oral route being preferred.

Typical compositions include a compound of formula I or a pharmaceutically acceptable acid addition salt thereof, associated with a pharmaceutically acceptable carrier. In making the compositions, conventional techniques for the preparation of pharmaceutical compositions may be used. For example, the active compound will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a ampoule, capsule, sachet, paper, or other container. When the carrier serves as a diluent, it may be solid, semi-solid, or liquid material which acts as a vehicle, excipient, or medium for the active compound. The active compound can be adsorbed on a granular solid container for example in a sachet. Some examples of suitable carriers are water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, gelatine, lactose, amylose, magnesium stearate, talc, silicic acid, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, hydroxymethylcellulose and polyvinylpyrrolidone.

The pharmaceutical preparations can be sterilized and mixed, if desired, with auxiliary agents, emulsifiers, salt for influencing osmotic pressure, buffers and/or coloring substances and the like, which do not deleteriously react with the active compounds.

For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil.

Tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like are particularly suitable for oral application. Preferable carriers for tablets, dragees, or capsules include lactose, corn starch, and/or potato starch. A syrup or elixir can be used in cases where a sweetened vehicle can be employed.

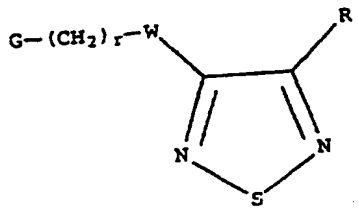
Generally, the compounds are dispensed in unit form comprising from about 1 to about 100 mg in a pharmaceutically acceptable carrier per unit dosage.

A typical tablet, appropriate for use in this method, may be prepared by conventional tabletting techniques and contains:

Active compound	5.0 mg
Lactosum	67.8 mg Ph.Eur.
Avicel®	31.4 mg
Amberlite®	1.0 mg
Magnesii stearas	0.25 mg Ph. Eur.

CLAIMS

1. A method of inhibiting squalene synthetase in a subject in need thereof comprising administering to said subject an effective amount of a compound of formula I



(I)

wherein

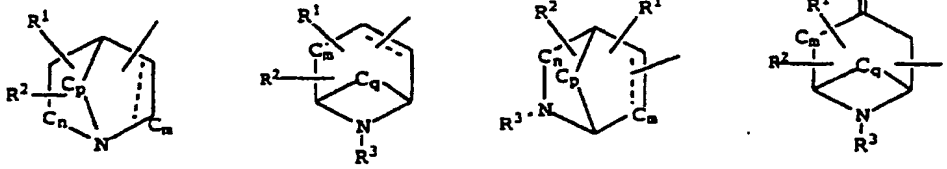
W is oxygen or sulphur; and

R is R^4, $-OR^4$, $-SR^4$, $-SOR^4$, $-SO_2R^4$, C_{3-10}-cycloalkyl, C_{4-12}-(cycloalkylalkyl), -Z-C_{3-10}-cycloalkyl or -Z-C_{4-12}-(cycloalkylalkyl), wherein Z is oxygen or sulphur, R^4 is C_{1-15}-alkyl, C_{2-15}-alkenyl or C_{2-15}-alkynyl, each of which is optionally substituted with one or more halogen(s), $-CF_3$, -CN, Y, phenyl or phenoxy, wherein phenyl or phenoxy is optionally substituted with halogen, -CN, C_{1-4}-alkyl, C_{1-4}-alkoxy, $-OCF_3$, $-CF_3$, $-CONH_2$ or $-CSNH_6$, and Y is as defined below; or

R is phenyl or benzyloxycarbonyl, each of which is optionally substituted with halogen, -CN, C_{1-4}-alkyl, C_{1-4}-alkoxy, $-OCF_3$, $-CF_3$, $-CONH_2$ or $-CSNH_2$; or

R is -Z-Y, $-O-R^5-Z-Y$, $-S-R^5-Z-Y$, $-O-R^5-Z-R^4$ or $-S-R^5-Z-R^4$, wherein Z is oxygen or sulphur, R^5 is C_{1-15}-alkylene, C_{2-15}-alkenylene or C_{2-15}-alkynylene, R^4 is as defined above, and Y is a 5 or 6 membered heterocyclic group containing one to four N, O or S atom(s) or a combination thereof, which heterocyclic group is optionally substituted at carbon and/or nitrogen atom(s) with C_{1-6}-alkyl, $-CF_3$, phenyl, benzyl or thienyl, or a carbon atom in the heterocyclic group together with an oxygen atom form a carbonyl group, or which heterocyclic group is optionally fused with a phenyl group; and

G is selected from one of the following azabicyclic ring systems



wherein R^1 and R^2 may be present at any position, including the point of attachment of the $(CH_2)_r$-W-group, and independently are hydrogen, C_{1-5}-alkyl, C_{2-5}-alkenyl, C_{2-5}-alkynyl, C_{1-10}-alkoxy, C_{1-5}-alkyl substituted with -OH, halogen, $-NH_2$, carboxy or phenyl; and

R^3 is hydrogen, C_{1-5}-alkyl, C_{2-5}-alkenyl or C_{2-5}-alkynyl; and

n is 0, 1 or 2; and

m is 0, 1 or 2; and

p is 0, 1 or 2; and

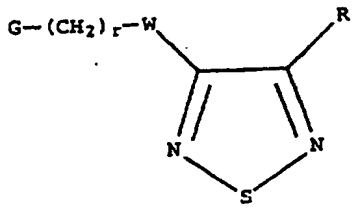
q is 1 or 2; and

r is 0,1 or 2; and

..... is a single or double bond;

or a pharmaceutically acceptable salt thereof.

2. A method of inhibiting squalene synthetase in a subject in need thereof comprising administering to said subject an effective amount of a compound of formula I



(I)

wherein

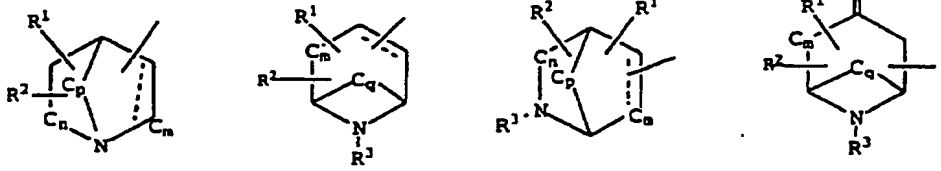
W is oxygen or sulphur; and

R is R^4, $-OR^4$, $-SR^4$, $-SOR^4$, $-SO_2R^4$, C_{3-10}-cycloalkyl, C_{4-12}-(cycloalkylalkyl), -Z-C_{3-10}-cycloalkyl or -Z-C_{4-12}-(cycloalkylalkyl), wherein Z is oxygen or sulphur, R^4 is C_{1-15}-alkyl, C_{2-15}-alkenyl or C_{2-15}-alkynyl, each of which is substituted with one or more halogen(s), $-CF_3$, -CN, Y, phenyl or phenoxy, wherein phenyl or phenoxy is optionally substituted with halogen, -CN, C_{1-4}-alkyl, C_{1-4}-alkoxy, $-OCF_3$, $-CF_3$, $-CONH_2$ or $-CSNH_6$, and Y is as defined below; or

R is phenyl or benzyloxycarbonyl, each of which is optionally substituted with halogen, -CN, C_{1-4}-alkyl, C_{1-4}-alkoxy, $-OCF_3$, $-CF_3$, $-CONH_2$ or $-CSNH_2$; or

R is -Z-Y, -O-R^5-Z-Y, -S-R^5-Z-Y, -O-R^5-Z-R^4 or -S-R^5-Z-R^4, wherein Z is oxygen or sulphur, R^5 is C_{1-15}-alkylene, C_{2-15}-alkenylene or C_{2-15}-alkynylene, R^4 is as defined above, and Y is a 5 or 6 membered heterocyclic group containing one to four N, O or S atom(s) or a combination thereof, which heterocyclic group is optionally substituted at carbon and/or nitrogen atom(s) with C_{1-6}-alkyl, $-CF_3$, phenyl, benzyl or thienyl, or a carbon atom in the heterocyclic group together with an oxygen atom form a carbonyl group, or which heterocyclic group is optionally fused with a phenyl group; and

G is selected from one of the following azabicyclic ring systems



wherein R^1 and R^2 may be present at any position, including the point of attachment of the $(CH_2)_r$-W-group, and independently are hydrogen, C_{1-5}-alkyl, C_{2-5}-alkenyl, C_{2-5}-alkynyl, C_{1-10}-alkoxy, C_{1-5}-alkyl substituted with -OH, halogen, $-NH_2$, carboxy or phenyl; and

R^3 is hydrogen, C_{1-5}-alkyl, C_{2-5}-alkenyl or C_{2-5}-alkynyl; and

n is 0, 1 or 2; and

m is 0, 1 or 2; and

p is 0, 1 or 2; and

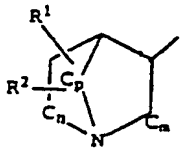
q is 1 or 2; and

r is 0,1 or 2; and

..... is a single or double bond;

or a pharmaceutically acceptable salt thereof.

3. The method according to claim 1 or 2 wherein G in formula I is the ring system



wherein R^1 and R^2 are as defined in claim 1, and m and n are 1, and p is 2; or a pharmaceutically acceptable salt thereof.

4. The method according to anyone of the preceding claims wherein the compound is selected from the following:

(±)-3-Methoxy-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-Ethoxy-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-Propyloxy-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-Butyloxy-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-Pentyloxy-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-Hexyloxy-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-(4-Methylpentyloxy)-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-Propylthio-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-Butylthio-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-Pentylthio-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(S)-3-Pentylthio-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-Hexylthio-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-(3,3-Dimethylbutylthio)-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-(2-(5-(2-Thienyl)thienyl)thio)-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-(2-(2-Thienylthio)ethylthio)-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-(2-Thienylthio)-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-(2,2,3,3,3-Pentafluoropropylthio)-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-(3-(2-Thienyl)propylthio)-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-Butylthio-4-((1-azabicyclo[2.2.2]octan-3-yl)methoxy)-1,2,5-thiadiazole,

(±)-Exo-3-pentylthio-4-(1-azabicyclo[3.2.1]octyl-6-oxy)-1,2,5-thiadiazole,

(±)-Endo-3-pentylthio-4-(1-azabicyclo[3.2.1]octyl-6-oxy)-1,2,5-thiadiazole,

(±)-Endo-3-butyloxy-4-(1-azabicyclo[2.2.1]heptyl-3-oxy)-1,2,5-thiadiazole,

(±)-Exo-3-butyloxy-4-(1-azabicyclo[2.2.1]heptyl-3-oxy)-1,2,5-thiadiazole,

(R)-3-Pentylthio-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-(4-Methylpentylthio)-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-(3-Phenylpropylthio)-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-(4-Cyanobenzylthio)-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-(4-Fluorobenzylthio)-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-(2-Phenylethylthio)-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-(2-Phenyloxyethylthio)-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

Endo-3-butyloxy-4-(N-methyl-8-azabicyclo[3.2.1]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-Exo-3-butyloxy-4-(6-(N-methyl-8-azabicyclo[3.2.1]octan-3-onoxy))1,2,5-thiadiazole,

(±)-Endo-3-(4-cyanobenzylthio)-4-(1-azabicyclo[3.2.1]octyl-6-oxy)-1,2,5-thiadiazole,

(±)-3-(2-(2-Thio-5-trifluoromethylthienyl)ethylthio)-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-(2-(2-(5-(2-Thienyl)thienyl)thio)ethylthio)-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-(3-N-(2-Thiazolidonyl)propylthio)-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

3-Butylthio-4-(exo-2-azabicyclo[2.2.2]oct-6-yloxy)-1,2,5-thiadiazole,

Endo-3-(3-Butylthio-1,2,5-thiadiazol-4-yloxy)-1-azabicyclo[2.2.1]heptane,

Endo-3-(3-propylthio-1,2,5-thiadiazol-4-yloxy)-1-azabicyclo[2.2.1]heptane,

Endo-3-(3-Propylsulfonyl-1,2,5-thiadiazol-4-yloxy)-1-azabicyclo[2.2.1]heptane,

Endo-3-(3-(3-(4-Fluorophenyl)-2-propynyl-1-oxy)-1,2,5-thiadiazol-4-yloxy)-1-azabicyclo[2.2.1]heptane,

Endo-3-(3-(3-phenyl-2-propynyl-1-oxy)-1,2,5-thiadiazol-4-yloxy)-1-azabicyclo-[2.2.1]heptane,

Endo-3-(3-Trifluoropropylthio-1,2,5-thiadiazol-4-yloxy)-1-azabicyclo[2.2.1]heptane,

Endo-3-(3-Trifluorobutylthio-1,2,5-thiadiazol-4-yloxy)-1-azabicyclo[2.2.1]heptane,

Endo-3-(3-(4-Cyanobenzylthio)-1,2,5-thiadiazol-4-yloxy)-1-azabicyclo[2.2.1]heptane,

Exo-3-(3-Propylthio-1,2,5-thiadiazol-4-yloxy)-1-azabicyclo[3.3.1]nonane,

Exo-3-(3-Butylthio-1,2,5-thiadiazol-4-yloxy)-1-azabicyclo[3.3.1]nonane,

or a pharmaceutically acceptable salt thereof.

5. The method according to anyone of the preceding claims wherein the compound is selected from the following:

(±)-3-Methoxy-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-Ethoxy-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-Propyloxy-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-Butyloxy-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-Pentyloxy-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-Hexyloxy-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-(4-Methylpentyloxy)-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-Propylthio-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-Butylthio-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-Pentylthio-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(S)-3-Pentylthio-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-Hexylthio-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-(3,3-Dimethylbutylthio)-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-(2-(5-(2-Thienyl)thienyl)thio)-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-(2-(2-Thienylthio)ethylthio)-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-(2-Thienylthio)-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-(2,2,3,3,3-Pentafluoropropylthio)-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-(3-(2-Thienyl)propylthio)-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-Butylthio-4-((1-azabicyclo[2.2.2]octan-3-yl)methoxy)-1,2,5-thiadiazole,

(R)-3-Pentylthio-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-(4-Methylpentylthio)-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-(3-Phenylpropylthio)-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-(4-Cyanobenzylthio)-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-(4-Fluorobenzylthio)-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-(2-Phenylethylthio)-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-(2-Phenyloxyethylthio)-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-(2-(2-Thio-5-trifluoromethylthienyl)ethylthio)-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-(2-(2-(5-(2-Thienyl)thienyl)thio)ethylthio)-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

(±)-3-(3-N-(2-Thiazolidonyl)propylthio)-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-thiadiazole,

3-Butylthio-4-(exo-2-azabicyclo[2.2.2]oct-6-yloxy)-1,2,5-thiadiazole,

or a pharmaceutically acceptable salt thereof.

6. A method of treating hypercholesterolemia in a subject in need thereof comprising administering to said subject an effective amount of a compound according to claim 1.

7. A method of treating hypercholesterolemia in a subject in need thereof comprising administering to said subject an effective amount of a compound according to claim 2.

8. A method of treating hypercholesterolemia in a subject in need thereof comprising administering to said subject an effective amount of a compound according to claim 3.

9. A method of treating hypercholesterolemia in a subject in need thereof comprising administering to said subject an effective amount of a compound according to claim 4.

10. A method of treating hypercholesterolemia in a subject in need thereof comprising administering to said subject an effective amount of a compound according to claim 5.

11. The use of a compound according to claim 1 or a pharmaceutically acceptable salt thereof for the preparation of a medicament for inhibiting squalene synthetase.

12. The use of a compound according to claim 1 or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treatment of hypercholesterolemia.

13. The use of a compound according to claim 2 or a pharmaceutically acceptable salt thereof for the preparation of a medicament for inhibiting squalene synthetase.

14. The use of a compound according to claim 2 or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treatment of hypercholesterolemia.

15. The use of a compound according to claim 3 or a pharmaceutically acceptable salt thereof for the preparation of a medicament for inhibiting squalene synthetase.

16. The use of a compound according to claim 3 or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treatment of hypercholesterolemia.

17. The use of a compound according to claim 4 or a pharmaceutically acceptable salt thereof for the preparation of a medicament for inhibiting squalene synthetase.

18. The use of a compound according to claim 4 or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treatment of hypercholesterolemia.

19. The use of a compound according to claim 5 or a pharmaceutically acceptable salt thereof for the preparation of a medicament for inhibiting squalene synthetase.

20. The use of a compound according to claim 5 or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treatment of hypercholesterolemia.